Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Chan JK, Brady MF, Penson RT, et al. Weekly vs. every-3-week paclitaxel and carboplatin for ovarian cancer. N Engl J Med 2016;374:738-48. DOI: 10.1056/NEJMoa1505067

Supplementary appendix

Acknowledgements

This study was supported by National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical and Data Center (CA 37517) and the NRG Oncology Grant 1 U10 CA180822. We thank Genentech for their generous support. We are indebted to all the dedicated physicians, nurses, study staff their contributions and most of all the patients and families for their participation.

The following institutions participated in this study:

Roswell Park Cancer Institute, University of Alabama at Birmingham, Duke University, Abington Memorial Hospital, Walter Reed National Military Medical Center, Wayne State University, University of Minnesota, Northwestern University, University of Mississippi, University of Colorado Cancer Center, University of California at Los Angeles, Fred Hutchinson Cancer Research Center, University of Pennsylvania, University of Cincinnati, University of North Carolina at Chapel Hill, University of Iowa Hospitals and Clinics, University of Texas Southwestern Medical Center, Indiana University, Wake Forest University, University of California Medical Center at Irvine, Rush University Medical Center, University of Pittsburgh, State University of New York Downstate Medical Center, University of Kentucky, University of New Mexico Cancer Center, Cleveland Clinic Foundation, Stony Brook University Medical Center, Washington University, Memorial Sloan Kettering Cancer Center, Cooper Hospital University Medical Center, Ohio State University Medical Center, MD Anderson Cancer Center, University of Massachusetts Memorial Health Care, Fox Chase Cancer Center, Women's Cancer Center of Nevada, University of Oklahoma Health Sciences Center, University of Virginia, University of Chicago, Mayo Clinic, Case Western Reserve University, Moffitt Cancer Center and Research Institute, Yale University, University of Wisconsin Hospital and Clinics, Cancer Trials Support Unit, Women and Infants Hospital, Seoul National University Hospital, The Hospital of Central Connecticut, Georgia Center for Oncology, Gynecologic Oncology of West Michigan, Aurora Cancer Center, UCSF-Mount Zion, St. Joseph's Hospital and Medical Center, Carolinas Medical Center, and Consortium Community Clinical Oncology Program.

We would like to thank all participants and their significant others, the teams of physicians, nurses, and research coordinators for their dedication, and Anne Reardon, Kim Blaser, and Meg Colahan for their administrative assistance.

Study Enrollment Criteria - eligibility

1. Primary Surgery and Neoadjuvant Chemotherapy with Interval Cytoreductive Surgery Patients:
    - **a.** Primary Surgery Patients:
        - **i.** Patients with newly diagnosed, previously untreated stage III patients with macroscopic residual or any stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer after surgical staging and maximal cytoreductive effort with macroscopic residual disease were eligible. On April 2011, after enrolling 102 patients we included those with stage III disease and no residual lesions greater than 1 cm and those with stage II disease given the closure of a competing trial, GOG-252. Then on June 2011, after 194 patients were enrolled, the eligibility was broadened to allow patients who chose neoadjuvant chemotherapy.
        - **ii.** FIGO stage is assessed following the completion of initial abdominal surgery, appropriate imaging studies and with appropriate tissue available for histologic evaluation. The minimum surgery required is an abdominal surgery providing tissue for histologic evaluation and establishing and documenting the primary site and stage. If additional surgery was performed, it should have been in accordance with appropriate surgery for ovarian or peritoneal carcinoma described in the GOG Surgical Procedures Manual (https://gogmember.gog.org/manuals/pdf/surgman.pdf).
    - **b.** Neoadjuvant Chemotherapy (NAC) with Interval Cytoreductive Surgery (ICS) Patients:
        - **i.** For patients undergoing NAC-ICS, a core tissue (not fine needle aspiration) biopsy is required. The tissue must be consistent with a müllerian origin. Patients will require documentation of at least stage II or extraovarian sites of disease acquired via imaging or surgery (without attempt at cytoreduction).
    - c. ACRIN 6695 eligible patients.
        - i. Patients must have measurable disease. At least one target lesion must have a minimum length of 1 cm in both the long and short axis (determined at the local site). For primary surgery patients, if no radiographic evidence of measurable disease is obtained prior to registration this can be based on surgical findings; imaging then would need to be completed in the 14 days between GOG registration and chemotherapy initiation. (Patients enrolled after February 8, 2012 must participate in the ACRIN 6695 component at ACRIN-qualified institutions) (04/30/2012) (10/22/2012) After GOG registration, the American College of Radiology [ACR] Imaging Core Laboratory will

confirm target lesion as required per protocol. The GOG-eligibility (RECIST) scan and baseline T0 perfusion CT scans will be reviewed prior to the intermediate T1 perfusion CT time point.

2. Patients with the following histologic epithelial cell types are eligible: Serous, endometrioid, clear cell, mucinous adenocarcinoma, undifferentiated carcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.). However, the histologic features of the tumor must be compatible with a primary Müllerian epithelial adenocarcinoma. Patients may have co-existing fallopian tube carcinoma in-situ so long as the primary origin of invasive tumor is ovarian, peritoneal or fallopian tube. Of note, patients with clear cell and mucinous tumors will be eligible unless there is a higher priority protocol.

   Following a post-enrollment centralized pathologic review, 22 enrolled patients were deemed ineligible. Nine had insufficient documentation of their primary tumor site, 2 had a second primary site, 3 had an invalid histology, 4 had an inappropriate stage of disease, and 4 had inadequate staging surgery. All of these cases were included in the analysis of treatment efficacy.

3. Patients must have adequate:
   a. Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl. This ANC cannot have been induced or supported by granulocyte colony stimulating factors.
   b. Platelets greater than or equal to 100,000/mcl.
   c. Renal function: Creatinine $\leq$ 1.5 x institutional upper limit normal (ULN).
   d. Hepatic function: Bilirubin less than or equal to 1.5 x ULN; SGOT less than or equal to 3 x ULN and alkaline phosphatase less than or equal to 2.5 x ULN.
   e. Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE Grade 1.
4. Patients must have a GOG Performance Status of 0, 1, or 2.
5. Patients must be entered within 12 weeks of diagnostic/staging surgery.
6. Patients who have met the pre-entry requirements specified in Section 7.0 of the Master Protocol.
7. An approved informed consent and authorization permitting release of personal health information and must be signed by the patient or guardian.

**** Only applies for patients who elect to receive bevacizumab**

** Patients in this trial may receive ovarian estrogen +/- progestin replacement therapy as indicated at the lowest effective dose(s) for

control of menopausal symptoms at any time, but not high-dose progestins for management of anorexia while on protocol-directed therapy or prior to disease progression due to thrombophlebitis risk.**

3.19** Patients must have adequate blood coagulation parameters: PT such that international normalized ratio (INR) is $\leq$ 1.5 (or an in-range INR, usually between 2 and 3, if a patient is on a stable dose of therapeutic warfarin for management of venous thrombosis including pulmonary thrombo-embolus) and a PTT $<$ 1.2 times the upper limit of normal. (Heparin, lovenox or alternative anticoagulants are acceptable.)**

3.110 All patients enrolled into GOG-0262 at sites where ACRIN 6695 is open will be enrolled in the advanced imaging protocol. Patients receiving adjuvant or neoadjuvant chemotherapy are eligible for ACRIN 6695. **The following sentence does not apply to those patients entered after 02/08/2012:** If a patient declines to participate in the perfusion imaging portion of the protocol, a clinical rationale for declination of imaging form will be completed as part of the data submission for ACRIN 6695. **(06/20/2011)**

Study Enrollment Criteria - ineligibility

1. Patients with a current diagnosis of borderline epithelial ovarian tumor (formerly "tumors of low malignant potential") or recurrent invasive epithelial ovarian, primary peritoneal or fallopian tube cancer treated with surgery only (such as patients with stage I-A or I-B low grade epithelial ovarian or fallopian tube cancers) are not eligible. Patients with a prior diagnosis of a borderline tumor that was surgically resected and who subsequently develop an unrelated, new invasive epithelial ovarian, peritoneal primary or fallopian tube cancer are eligible, provided that they have not received prior chemotherapy for any ovarian tumor.
2. Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis. Prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.
3. Patients who have received prior chemotherapy for any abdominal or pelvic tumor including neo-adjuvant chemotherapy for their ovarian, primary peritoneal or fallopian tube cancer. Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease.

4. Patients who have received any targeted therapy (including but not limited to vaccines, antibodies, tyrosine kinase inhibitors) or hormonal therapy for management of their epithelial ovarian, fallopian tube or peritoneal primary cancer.
5. Patients with synchronous primary endometrial cancer, or a past history of primary endometrial cancer, unless all of the following conditions are met: Stage not greater than I-A, grade 1 or 2, no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell or other FIGO grade 3 lesions.
6. With the exception of non-melanoma skin cancer, patients with other invasive malignancies who had (or have) any evidence of the other cancer present within the last five years or whose previous cancer treatment contraindicates this protocol therapy.
7. Patients with acute hepatitis or active infection that requires parenteral antibiotics.
8. Patients with clinically significant cardiovascular disease. This includes:
    a. Myocardial infarction or unstable angina < 6 months prior to registration.
    b. New York Heart Association (NYHA) Grade II or greater congestive heart failure (Appendix II).
    c. Serious cardiac arrhythmia requiring medication. This does not include asymptomatic, atrial fibrillation with controlled ventricular rate.
9. Patients who are pregnant or nursing. To date, no fetal studies in animals or humans have been performed. (For patients who elect to receive bevacizumab: The possibility of harm to a fetus is likely. Bevacizumab specifically inhibits VEGF, which is responsible for formation of new blood vessels during development, and antibodies can cross the placenta. Therefore, bevacizumab should not be administered to pregnant women. Subjects will be apprised of the large potential risk to a developing fetus. It is not known whether bevacizumab is excreted in human milk. Because many drugs are excreted in human milk, bevacizumab should not be administered to nursing women. Patients of childbearing potential must agree to use contraceptive measures during study therapy and for at least six months after completion of bevacizumab therapy.)
10. Patients under the age of 18.
11. Patients who have received prior therapy with any anti-VEGF drug, including bevacizumab.
12. Patients with medical history or conditions not otherwise previously specified which in the opinion of the investigator should exclude participation in this study. The investigator should feel free to consult the SDC Randomization Desk for uncertainty in this regard.
13. Patients with known allergy to cremophor or polysorbate 80. ****Only applies to patients who elect to receive bevacizumab**

14. ** Patients with serious non-healing wound, ulcer, or bone fracture. This includes history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 28 days. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations (see Section 7.1).**
15. ** Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels.**
16. ** Patients with history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within six months of the first date of treatment on this study. **
17. ** Patients with CTCAE Grade 2 or greater peripheral vascular disease [at least brief (<24 hours) episodes of ischemia managed non-surgically and without permanent deficit].**
18. ** Patients with a history of CVA within six months.**
19. ** Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.**
20. ** Patients with clinically significant proteinuria. Urine protein should be screened by urine protein-creatinine ratio (UPCR). The UPCR has been found to correlate directly with the amount of protein excreted in a 24 hour urine collection.[73-77] Specifically, a UPCR of 1.0 is equivalent to 1.0 gram of protein in a 24-hour urine collection. Obtain at least 4 ml of a random urine sample in a sterile container (does not have to be a 24-hour urine). Send sample to lab with request for urine protein and creatinine levels [separate requests]. The lab will measure protein concentration (mg/dL) and creatinine concentration (mg/dL). The UPCR is derived as follows: protein concentration (mg/dL)/creatinine (mg/dL). Patients must have a UPCR < 1.0 to allow participation in the study.**
21. ** Patients with or with anticipation of invasive procedures as defined below:
22. ** Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to the first date of bevacizumab therapy (cycle 2).**
23. ** Major surgical procedure anticipated during the course of the study. This includes, but is not limited to abdominal surgery (laparotomy or laparoscopy) prior to disease progression as defined in section 8, such as colostomy or enterostomy reversal, secondary cytoreductive surgery, or second look surgery. **
24. ** Any tissue biopsy, such as a core biopsy, within 7 days prior to the first date of bevacizumab therapy (cycle 2).**
25. ** Patients with clinical symptoms or signs of gastrointestinal obstruction **and** who require parenteral hydration and/or nutrition.**

26.** Patients with metastatic tumor in the parenchyma of the liver or lungs with proximity to large vessels which could make the patients at high risk of lethal hemorrhage during treatment with bevacizumab (ie. hemoptysis, liver rupture).**

§§ This section applies to the ACRIN 6695 imaging portion of the trial; eligibility assessment for target lesion (Section 3.2112 below) will be completed after registration to the GOG trial and completion of the baseline T0 CT scan. (06/20/2011) (10/22/2012)

Patients enrolled after February 8, 2012 must participate in the ACRIN 6695 component at ACRIN-qualified sites. Patients whose target lesion meets the protocol criteria for ACRIN 6695 will continue on both the GOG-0262 treatment study and the ACRIN 6695 imaging study. Patients whose target lesion does not meet the protocol criteria for ACRIN 6695 will continue on the GOG-0262 treatment study but will be considered off-study for ACRIN 6695. The ACR Imaging Core Lab or ACRIN Headquarters staff will inform the site whether the participant will continue with additional perfusion CT imaging after baseline T0 per ACRIN 6695 study protocol.

(04/30/2012) (10/22/2012)

ACRIN 6695 Eligible Patients (10/22/2012)

3.2112**§§** Confirmation of ACRIN 6695 eligibility after the baseline T0 perfusion CT will be assessed by the ACR Imaging Core Lab: At least one target lesion must have a minimum length of 1 cm in both the long and short axis (as determined by the local site), at least half of the target lesion must have attenuation greater than or equal to 10 Hounsfield Units (HU) on the unenhanced CT, and at least half of the lesion must have maximum enhancement greater than or equal to 5 HU in the perfusion CT scan (as determined by the ACR Imaging Core Lab).

ACRIN 6695 Ineligible Patients (10/22/2012)

3.2113**§§** Patients with contraindication to iodinated contrast for perfusion CT imaging. **(06/20/2011)**

3.2114**§§** Patients who receive Metformin within 48 hours before perfusion CT imaging. **(06/20/2011)**

FIGO STAGE GROUPING FOR PRIMARY CARCINOMA OF THE OVARY

These categories are based on findings at clinical examination and/or surgical exploration. The histologic characteristics are to be considered in the staging, as are results of cytologic testing as far as effusions are concerned. It is desirable that a biopsy be performed on suspicious areas outside the pelvis.

Stage I

Growth limited to the ovaries.

Stage IA Growth limited to one ovary; no ascites.

No tumor on the external surface; capsule intact.

Stage IB Growth limited to both ovaries; no ascites.

No tumor on the external surfaces; capsules intact.

Stage IC* Tumor either Stage IA or IB but with tumor on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.

Stage II Growth involving one or both ovaries with pelvic extension.

Stage IIA Extension and/or metastases to the uterus and/or tubes.

Stage IIB Extension to other pelvic tissues.

Stage IIC* Tumor either Stage IIA or IIB but with tumor on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.

Stage III Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals Stage III. Tumor is limited to the true pelvis but with histologically verified malignant extensions to small bowel or omentum.

Stage IIIA Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.

Stage IIIB Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative.

Stage IIIC Abdominal implants >2 cm in diameter and/or positive retroperitoneal or inguinal nodes.

Stage IV Growth involving one or both ovaries with distant metastasis. If pleural effusion is present there must be positive cytologic test results to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV.

*In order to evaluate the impact on prognosis of the different criteria for allotting cases to Stage IC or IIC, it would be of value to know if rupture of the capsule was (1) spontaneous or (2) caused by the surgeon and if the source of malignant cells detected was (1) peritoneal washings or (2) ascites.

Gynecologic Oncology Group Performance Status Scale

0 – fully active.

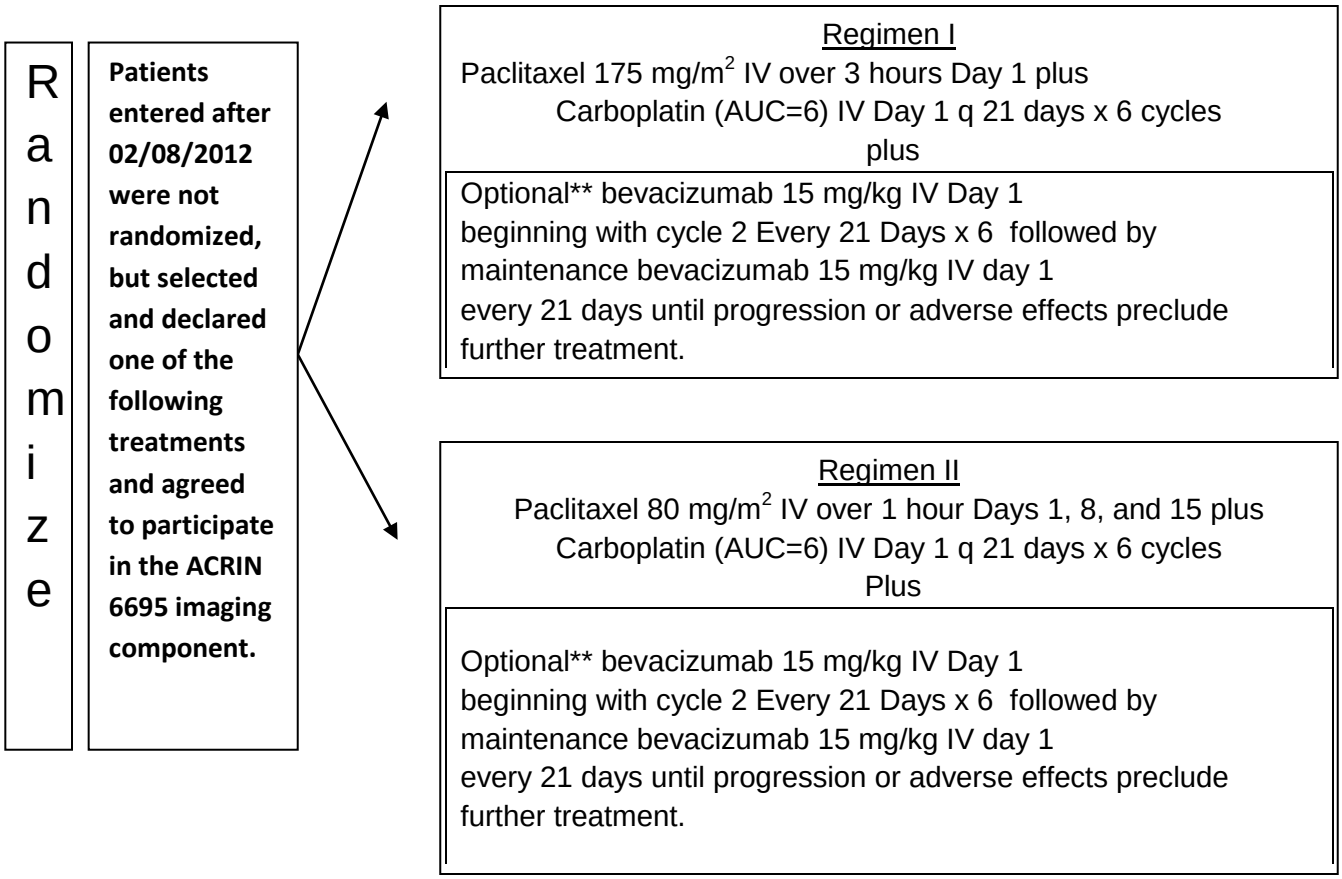
1 – restricted in physically strenuous activities, but ambulatory.

2 – ambulatory, capable of self-care; unable to work; up 50% of waking hour

3 – limited self-care; confined to bed or chair 50% of waking hours

4 – completely disabled; no self-care

Figure S1: Protocol Schema



*Patients undergoing neoadjuvant chemotherapy (NACT) with interval cytoreductive surgery (ICS) must be recorded prior to registration. After core needle biopsy to establish diagnosis, patients will receive 3 cycles of NACT with ICS between cycles 3 and 4, followed by 3 additional cycles of chemotherapy. If chosen, bevacizumab will be administered during cycles 2, 5, and 6, but omitted during cycles 1, 3 and 4

** Prior to enrolling onto this study, each patient will choose whether the study treatment will include concurrent and maintenance bevacizumab.

Disease Assessment Methods and Schedule

	Prior to Study Entry	Prior to Each Cycle	Every Other Cycle	Q3 months after completing treatment x 2 years, Q6 months x 3 years, then annually
History	@	x		x
Physical Exam	@	x		x
Performance Status	@	x		x
Quality of Life Questionnaire	#	#		#
Serum CA-125 Level	@		**x	**x
Radiographic Disease Assessment	@		**x	**x
Chest Imaging	@			
RECIST Tumor Measurements	@		**x	**x

@ Must be obtained within 28 days prior to initiating protocol therapy.
# Obtained at five time points: Prior to Cycle 1, prior to cycle 4 of protocol directed chemotherapy (~9 weeks from day 1 of cycle 1 if no longer receiving protocol directed treatment), 18 weeks from day 1 cycle 1, 36 weeks from day 1 cycle 1, and 63 weeks from day 1 cycle 1.
**Follow-Up Radiographic Assessment of Disease. In the absence of disease progression, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be repeated with the following schedule, <u>regardless of whether or not the patient had measurable disease on initial CT or MRI</u>:

a) After cycle 3 (before cycle 4) of paclitaxel-carboplatin
b) After cycle 6 of paclitaxel-carboplatin
c) After completion of carboplatin and paclitaxel, every 3 months for 2 years, then every 6 months for 3 years, then annually
d) During or after completion of all protocol therapy, as clinically indicated at any time for clinical suspicion of progressive disease, including rising serum CA-125 levels not meeting criteria for disease progression in and of themselves according to section 8.3 of the Master Protocol.

Treatment Modification

1. General Remarks :
   In order to maintain dose-intensity and cumulative dose-delivery on this study, reasonable efforts were made to minimize dose reduction and treatment delays as specified. Any patient whose treatment was delayed was evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. No dose escalation was planned for this study.

2. Delay of Subsequent Treatment
   If treatment was delayed more than 21 days for reasons of toxicity, then protocol-directed cytotoxic therapy was ended; patient may have, at discretion of treating physician, continue with non-protocol directed cytotoxic therapy (dose reductions and growth factors) for up to six total cycles of cytotoxic therapy, and if the patient opted for bevacizumab treatment, protocol bevacizumab may be continued with such therapy. If there were no contraindications, consolidation protocol-directed bevacizumab can still be administered.

3. Dose Modification for Bevacizumab
   There were no dose reductions for bevacizuamb. Treatment was to be interrupted or discontinued for certain adverse events as described below. If bevacizumab was interrupted for any reasons for more than four weeks (unless otherwise specified), the patient was to discontinue bevacizumab therapy on protocol.

4. General Guidelines for Hematologic Toxicity
   a. Treatment decisions were based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).
   b. Lower Limits for ANC and Platelet Count
      i. **With Cytotoxic Chemotherapy** – Day 1 of a subsequent cycle of cytotoxic chemotherapy were not administered until the ANC is ≥ 1,000 cells/mcl and the platelet count was ≥ 75,000/mcl. All treatment (including bevacizumab) was delayed for a maximum of three weeks until these values were achieved. Patients who failed to recover adequate counts within a three-week delay were no longer receiving protocol-directed cytotoxic therapy. If the patient opted to include bevacizumab with her study treatment, then bevacizumab may have been continued, provided there were not contraindications.
      Regimen II: The day 8 and 15 paclitaxel dose was not given unless the ANC was at least 500 cells/mcl and the platelet count at least 50,000/mcl. If not given, these doses were omitted and not made up.
   c. **During Consolidation (if opted for bevacizumab)**, day 1 bevacizumab treatment was not to be given until the ANC is ≥ 1,000 cells/mcl and the platelet count was ≥ 75,000/mcl. Treatment with bevacizumab was delayed for a maximum of three weeks until these values were achieved.

Patients who fail to recover adequate counts within a three-week delay no longer received any protocol-directed therapy.

5. Use of Hematopoietic Cytokines and Protective Agents
    a. It was anticipated that myelosuppression may be a significant side effect of each regimen. Myeloid growth factors (either filgrastim or pegfilgrastim) can be used (it is recommended that NCCN and/or ASCO guidelines be consulted). If myeloid growth factors were used, it was recommended that filgrastim (dose according to institutional standard) be administered daily subcutaneously starting 24-72 hours after the last dose of chemotherapy and continuing through hematopoietic recovery or pegfilgrastim be administered at 6 mg subcutaneously (one dose per treatment cycle) 24-72 hours after the last dose of chemotherapy. Administration of growth factors on the same day as chemotherapy was not recommended. Pegfilgrastim was not recommended for chemotherapy regimens given less than every 2 weeks.
    b. Patients were NOT to receive prophylactic thrombopoietic agents.
    c. Patients may have received erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians were made aware of the prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which noted that there was a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents were administered only to avoid red blood cell transfusions. They were not indicated in patients being treated with curative intent. They do not alleviate fatigue or increase energy. They should NOT be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.
    d. Patients may NOT have received amifostine or other protective reagents.

6. Dose Modifications for Paclitaxel and Docetaxel
    a. Regimen I: There was to be no dose modifications for paclitaxel based on hematologic toxicity. Dose modifications for docetaxel are according to Tables A and B below.
    b. Regimen II: The day 8 and 15 paclitaxel dose was not given unless the ANC was at least 500 cells/mcl and the platelet count is at least 50,000/mcl. If not given, these doses were omitted and not made up.
    c. Modifications for Hematologic Toxicity (Nadirs)
        i. Initial occurrence of dose-limiting neutropenia (defined above) or dose limiting thrombocytopenia (defined above) were handled according to Tables S2 or S3.
        ii. Dose-Limiting Neutropenia (DLT-ANC) was defined by the occurrence of febrile neutropenia, prolonged Grade 4 neutropenia persisting $\geq$ 7 days, delay of treatment for more than 7 days

because of neutropenia, ANC<1000cells/mcl on day 1, or omission of day 8 or day 15 paclitaxel on Regimen II because of neutropenia. Febrile neutropenia was defined within the CTCAE as a disorder characterized by an ANC <1000/mcl and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour.

iii. Dose-limiting thrombocytopenia (DLT-PLT) was defined by any occurrence of Grade 4 thrombocytopenia (<25,000/mcl) or bleeding associated with Grade 3 thrombocytopenia (25,000 to <50,000/mcl), delay of treatment on day 1 of a cycle by more than 7 days because of thrombocytopenia, platelet count of <75,000/mcl on day 1, or inability to give day 8 or day 15 paclitaxel on Regimen II due to thrombocytopenia. There were no modifications for uncomplicated Grade 3 thrombocytopenia except as above.

Modification Instructions for Dose-Limiting Hematologic Toxicity

Regimen I				
DLT ANC	**DLT PLT**	**First Occurrence**	**Second Occurrence**	**Third Occurrence**
Yes	**No**	Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel)	Add G-CSF and maintain all current drug doses.	Discontinue Protocol-Directed Cytotoxic Therapy
Yes	**Yes**	Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel)	Add G-CSF and Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel)	Discontinue Protocol-Directed Cytotoxic Therapy
No	**Yes**	Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel)	Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel).	Discontinue Protocol-Directed Cytotoxic Therapy

Modification Instructions for Dose-Limiting Hematologic Toxicity

Regimen II				
DLT ANC	**DLT PLT**	**First Occurrence**	**Second Occurrence**	**Third Occurrence**
Yes	**No**	Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel)	Omit day 15 paclitaxel and administer G-CSF starting after day 8 paclitaxel (if patient on docetaxel, start G-CSF 24 hours after docetaxel with no further dose reduction)	Reduce caboplatin one AUC, and give G-CSF after day 8 paclitaxel. Fourth occurrence: Discontinue Part A Protocol Directed Cytotoxic Therapy.
Yes	**Yes**	Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel)	Omit day 15 paclitaxel and administer G-CSF starting after day 8 paclitaxel (if patient on docetaxel, start G-CSF 24 hours after docetaxel) and reduce carboplatin one AUC until (and docetaxel by 10 mg/m^2 if pt on docetaxel)	Discontinue Part A Protocol-Directed Cytotoxic Therapy
No	**Yes**	Reduce carboplatin one AUC unit.	Decrease carboplatin one AUC unit.	Discontinue Part A Protocol-Directed Cytotoxic Therapy

7. Adjustments for Non-Hematologic Toxicity
   Table S4 was used for dose level modifications for non-hematologic toxicity only as indicated specifically in the sections below.

Modifications for Non-Hematologic Toxicity

Drug	**Regimen Starting Dose**	**Regimen -1 Level**	**Regimen -2 level**
Paclitaxel (3 week)	175 mg/m^2	135 mg/m^2	110 mg/m^2
Paclitaxel (weekly)	80 mg/m^2	70 mg/m^2	60 mg/m^2
Carboplatin	6.0	5.0	4.0
Docetaxel (3 week)	75 mg/m^2	65 mg/m^2	55 g/m^2

a. Grade 2 (or greater) peripheral neuropathy required reduction of one dose level in paclitaxel and delay in all subsequent protocol-directed therapy for a maximum of three weeks until recovered to Grade 1. If peripheral neuropathy failed to recover to Grade 1 by a maximum delay of three weeks from time therapy was due, or recurs, then paclitaxel should be withheld from all subsequent chemotherapy cycles, and docetaxel should be substituted. Patients on regimen II were to be effectively switched to regimen I using docetaxel. Weekly docetaxel was not to be used.
b. Hypertension. Patients receiving bevacizumab were monitored prior to each dose with measurement of blood pressure. Medication classes used for management of patients with hypertension receiving bevacizumab include angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers. The use of anxiolytics in conjunction with specific anti-hypertensive agents was not prohibited. The goal for blood pressure control should be consistent with general medical practice guidelines (i.e. $<$ 140/90 mmHg in general and $<$ 130/80 mmHg for patients with diabetes). For controlled hypertension, defined as systolic $\leq$ 160 mm Hg and diastolic $\leq$ 90 mm Hg, bevacizumab therapy was continued.
   i. For uncontrolled hypertension (systolic $>$ 160 mm Hg or diastolic $>$ 90) or symptomatic hypertension less than CTCAE Grade 4, cytotoxic chemotherapy was held for up to 1 week if indicated (see

below), with anti-hypertensive therapy initiated or continued. For treatment modification for Bevacizumab-related adverse events, please see Table S5.

1. During the period of combination chemotherapy, if the patient had opted to receive bevacizumab, if hypertension was controlled and symptomatic hypertension had resolved by one week after holding treatment, continue all therapy. For treatment modification for Bevacizumab-related adverse events, please see Table S5.
2. During the period of combination chemotherapy, if the patients had opted to receive bevacizumab, if hypertension remained uncontrolled or symptomatic hypertension, less than CTCAE Grade 4, persisted one week after holding treatment, the next treatment cycle should contain paclitaxel and carboplatin only, if applicable, as otherwise indicated in the protocol, with bevacizumab omitted. For treatment modification for Bevacizumab-related adverse events, please see Table S5.

c. Proteinuria. Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab. For treatment modification for Bevacizumab-related adverse events, please see Table S5.
d. Renal toxicity (associated with reduction in GFR) was not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule of each regimen. As such, there were no specific dose modifications for renal toxicity. However, the target AUC dose of carboplatin must be recalculated each cycle in any patient who developed renal insufficiency, defined by serum creatinine greater than 1.5 x institutional upper limit normal (ULN).
e. Intestinal obstruction. Bevacizumab was held for occurrence of CTCAE Grade 3 toxicity, until resolution to ≤CTCAE Grade 1 and permanently discontinued for occurrence of CTCAE Grade 4 toxicity. Since the development of intestinal obstruction could be a result of cancer progression, the investigator should take steps to evaluate such patients for the possibility of disease progression using clinical, laboratory and radiographic information as clinically indicated; in the event of disease progression, all protocol-directed therapy was discontinued.
f. Hepatic toxicity was not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule for each regimen. However, the development of Grade

3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin required reduction of one dose level in paclitaxel or reduction of docetaxel by 10 mg/m^2 and delay in subsequent therapy for a maximum of three weeks until recovered to Grade 1.

g. There were no dose modifications for alopecia, nausea, or constipation. It was recommended that routine medical measures be employed to manage nausea, constipation. Grade 3 diarrhea on day of planned treatment required holding of paclitaxel in patients on weekly paclitaxel and holding of docetaxel in patients on docetaxel. Any grade 3 diarrhea in patients on weekly paclitaxel mandated a one dose level reduction of paclitaxel in future cycles; in patients on docetaxel it required a 10 mg/m^2 dose reduction of docetaxel for future cycles. If the diarrhea was clearly infectious and had resolved, the above mandated dose reductions did not apply.

h. <u>Treatment Guidelines for Reversible Posterior Leukoencephalopathy Syndrome (RPLS):</u> Bevacizumab was held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS. Note: Resumption of bevacizumab may be considered in patients who have documented benefit from the agent, provided that RPLS was <u>mild</u> and has <u>completely</u> resolved clinically and radiographically within 2-4 weeks; decision to resume bevacizumab in these patients were to be discussed with the study chair and approved by the sponsor.

i. In general, the occurrence of a hypersensitivity reaction to paclitaxel, docetaxel, or bevacizumab was not considered a dose-limiting toxicity. Patients may be retreated at full doses after administration of medication to prevent hypersensitivity reactions, and adjustments in infusion rates should be made. However, if despite these safety measures repeat attempt at infusion of the inciting drug resulted in a recurrent hypersensitivity reaction, the inciting drug should be discontinued for the remainder of the study. In the event of any CTCAE Grade 3 or 4 allergic or infusion reaction to bevacizumab, bevacizumab was permanently discontinued.

j. Potential modifications for other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) required discussion with one of the study co-chairs except where noted below.

    i. Special Modifications Study Treatment: For any CTCAE Grade 3 non-hematologic adverse event (except controllable nausea/emesis) considered to be at least possibly related to study

treatment, protocol directed treatment was held until symptoms resolve to ≤ CTCAE Grade 1. If a CTCAE Grade 3 adverse event persists for > three weeks or recurs after resumption of therapy, the patient may have been taken off protocol directed treatment after consulting with the Study Chair. For any CTCAE Grade 4 non-hematologic adverse event (except controllable nausea/emesis), the patient may have been taken off protocol directed treatment therapy after consulting with the Study Chair.

Treatment Modification for Bevacizumab-Related Adverse Events

Event	**CTCAE. v4.0 Grade**	**Action to be Taken**
Allergic reactions **or** **Infusion-related reactions** **Or** **Anaphylaxis**	Grade 1-2	Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle. Subjects who experience bronchospasm (regardless of grade) should discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event (Arterial); arterial ischemia - Cardiac ischemia - Myocardial infraction - CNS ischemia (TIA, CVA) - any peripheral or visceral arterial	Grade 2 (new or worsening since bevacizumab	Discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab

Event	CTCAE. v4.0 Grade	Action to be Taken
ischemia/thrombosis		
Thromboembolic Event Venous)	[Note: Patients with lung cancer requiring therapeutic anticoagulation should discontinue bevacizumab]	
	Grade 3 OR asymptomatic Grade 4	▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2weeks, bevacizumab should be held until the full-dose anticoagulation period is over. ▪ If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during full-dose anticoagulation **IF** <u>all</u> of the criteria below are met: • The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) • The subject must not have had hemorrhagic events while on study • The subject must be on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. ▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 (symptomatic)	Discontinue bevacizumab
Hypertension*	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1 (SBP 120-139 mmHg or DBP80-	Consider increased BP monitoring; start anti-hypertensive medication if appropriate

Event	CTCAE. v4.0 Grade	Action to be Taken
	89 mm Hg)	
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)	Begin anti-hypertensive therapy and continue bevacizumab
	• Grade 2 symptomatic (SBP 140-160 mmHg or DBP 90-100 mm Hg) • Grade 3 (≥ SBP 160 mmHg or ≥ DBP 100 mmHg	• Start or adjust anti-hypertensive medication • Hold bevacizumab until symptoms resolve **AND** BP < 160/90mmHg
	Grade 4	Discontinue bevacizumab.
Heart Failure or LV dysfunction	Grade 3	Discontinue bevacizumab
	Grade 4	Discontinue bevacizumab
Proteinuria	[Proteinuria should be monitored by urine analysis for urine protein creatinine (UPC) ratio, prior to every other dose of bevacizumab.]**(02/06/2012)**	
	UPC ratio < 3.5 or 24-h urine protein < 3.5 gm	Continue bevacizumab. *Once 24-hour urine is <3.5gm, it is not necessary to repeat 24-hour urine for 2+ proteinuria.
	UPC ratio ≥ 3.5 or 24-h urine protein ≥ 3.5 gm	Hold bevacizumab until it UPC recovers to < 3.5, or 24-h urine protein < 3.5 gm. Discontinue bevacizumab if urine protein does not recover to < 3.5 after 8 weeks or

Event	CTCAE. v4.0 Grade	Action to be Taken
		bevacizumab interruption
	Nephrotic syndrome	Discontinue bevacizumab.
Hemorrhage (intracranial or pulmonary)	Grade 2-4	• Discontinue bevacizumab
	Grade 1	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and Hb is stable - there is no bleeding diathesis that would increase the risk of therapy • there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence
Hemorrhage (any other organ systems)	Grade 3	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and Hb is stable - there is no bleeding diathesis that would increase the risk of therapy - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy.
	Grade 4	Discontinue bevacizumab
RPLS (Reversible Posterior Leukoencephalopathy syndrome **or PRES** (Posterior Reversible Encephalopathy Syndrome)		• **Discontinue bevacizumab upon diagnosis of RPLS.**

Event	CTCAE. v4.0 Grade	Action to be Taken
Wound dehiscence requiring medical or surgical intervention		• **Discontinue bevacizumab**
Perforation (GI, or any other organ)		Discontinue bevacizumab
Fistula (GI, pulmonary or any other organ)		Discontinue bevacizumab
Obstruction of GI tract	G2 requiring medical intervention	• Hold bevacizumab until complete resolution
	G3-4	• Hold bevacizumab until complete resolution • If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion
Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	• Hold bevacizumab until symptoms resolve to ≤ grade 1
	Grade 4	• Discontinue bevacizumab • **Upon consultation with the study chair,** resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the G4 toxicity is transient, has recovered to ≤ grade 1 and unlikely to recur with retreatment.
• Non-clinically significant labs (e.g. Na <130 (CTCAE Grade 3) should NOT trigger holding Bevacizumab		

Assessment of Disease Response: RECIST version 1.1

Response and progression were evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). [1] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes were used in the RECIST criteria.

1. Measurable disease: Measurable lesions were defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam. All tumor measurements were to be recorded in decimal fractions of centimeters.

   Note: Tumor lesions that were situated in a previously irradiated area were not considered measurable unless progression was documented or a biopsy was obtained to confirm persistence at least 90 days following completion of radiation therapy.

2. Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis was measured and followed.

3. Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), were considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), were considered as non-measurable.

4. Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component met the definition of measurability described above. Blastic bone lesions were non-measurable.

5. Cystic lesions that met the criteria for radiographically defined simple cysts were not to be considered as malignant lesions (neither measurable nor non-measurable) since they were, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they met the definition of measurability described above. However, if non-cystic lesions were present in the same patient, these were preferred for selection as target lesions.

6. Baseline Documentation of Target and Non-Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, were to be identified as **target lesions** and recorded and measured at baseline. Target lesions were to be selected on the basis of their size (lesions

with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion did not lend itself to be reproducible measurement in which circumstance the next largest lesion that can be reproducibly measured were to be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions were calculated and reported as the baseline sum diameters. If lymph nodes were included in the sum, then only the short axis was added into the sum. The baseline sum diameters were used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions were to be identified as **non-target lesions** and were also to be recorded at baseline. Measurements of these lesions were not required, but the presence, absence, or in rare cases unequivocal progression of each were to be noted throughout follow-up.

7. Methods of Evaluation of Disease: All measurements were to be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations were to be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique were to be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation was preferred to evaluation by clinical examination unless the lesion(s) being followed could not be imaged but were assessable by clinical exam.
    a. Clinical lesions: Clinical lesions were considered measurable when they were superficial (e.g., skin nodules and palpable lymph nodes) and □10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, was recommended.

    b. Chest x-ray: Lesions on chest x-ray were acceptable as measurable lesions when they were clearly defined and surrounded by aerated lung. However, CT was preferred.

    c. Conventional CT and MRI: This guideline had defined measurability of lesions on CT scan based on the assumption that CT slice thickness was 5 mm or less. If CT scans had slice thickness greater than 5 mm, the minimum size for a measurable lesion was to be twice the slice thickness. MRI was also acceptable in certain situations (e.g. for body scans), but NOT lung.

8. Evaluation of Target Lesions

    a. Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduced in short axis to <10 mm.

b. Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

c. Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

d. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

e. Not evaluable (NE): When at least one target lesion was not evaluated at a particular time point.

9. Evaluation of Non-Target Lesions

a. Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis). If CA-125 was initially above the upper normal limit, it must have normalized for a patient to be considered in complete clinical response.

b. Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

c. Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

d. Not evaluable (NE): When at least one non-target lesion was not evaluated at a particular time point.

10. Evaluation of Biomarkers: Biomarker-based progression or recurrence involves assessing the patient's longitudinal CA-125 values. The definition of CA-125 progression or recurrence is based on the Gynecologic Cancer Intergroup criteria.[2] CA-125 based progression or recurrence is defined as one of the following conditions occurring:

a. CA-125 is within normal limits prior to treatment but subsequently rises to levels greater than or equal to two times the upper-limit of normal on two occasions at least one week apart.

b. CA-125 is elevated prior to treatment, does not normalize but rises to levels greater than or equal to twice its nadir value on two occasions at least one week apart.

c. CA-125 is elevated prior to treatment and returns to normal levels, but subsequently rises to levels greater than or equal to two times the upper limit of normal on two occasions at least one week apart.

d. When recurrence or progression was based on CA-125 criteria alone, radiographic imaging was to be obtained within 2 weeks after such progression was documented. If imaging criteria were met for progression, then the date of progression was defined as the date of the imaging study.

11. Evaluation of Best Overall (unconfirmed) Response The best overall response is the best time point response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum recorded since baseline). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria in some circumstances.

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

Lesions	**Non-Target Lesions**	**Biomarker CA-125**	**New Lesions**	**Time Point Response**
CR	CR	Within normal limits	No	CR
CR	Non-CR/Non-PD	Any value	No	PR
CR	Not evaluated	Any value	No	PR
PR	Non-PD or NE	Any value	No	PR
SD	Non-PD or NE	Any value	No	SD

NE	Non-PD	Any value	No	NE
PD	Any	Any value	Yes or No	PD
Any	PD	Any value	Yes or No	PD
Any	Any	PD	No	PD
Any	Any	Any value	Yes	PD

Time Point Response for Patients with only Non-Measurable Disease at baseline (i.e., Non-Target Disease)

Non-Target Lesions	**Biomarker CA-125**	**New Lesions**	**Time Point Response**
CR	Within normal limits	No	CR
CR	Above normal limits	No	Non-CR/non-PD
Non-CR/non-PD	Any value	No	Non-CR/non-PD
NE	Any value	No	NE
Unequivocal PD	Any value	Yes or No	PD
Any	PD	No	PD
Any	Any value	Yes	PD
** ‘Non-CR/non-PD’ was preferred over ‘stable disease’ for non-target disease since SD was increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured was not advised			

12. Best Overall Confirmed Response: Confirmation of CR and PR for determination of best overall response is required for studies with a primary endpoint that includes response.

Confirmed CR and PR for best overall confirmed response

Time Point Response **First time point**	**Time Point Response** **Subsequent time point**	**BEST overall confirmed response**
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

*If a CR was *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, made the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when

subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR would be changed to PR or SD and the best response would have been PR or SD.

For this study, the minimum criteria for SD duration was 8 weeks.

Patients with a global deterioration of health status requiring discontinuation of treatment or who die without objective evidence of disease progression at that time were to be reported to be off study treatment due to “symptomatic deterioration.” Every effort was to be made to document the objective progression even after discontinuation of treatment.

13. Duration of Response:

    a. Duration of overall response: The duration of overall response was measured from the time measurement criteria were met for CR or PR (whichever was first recorded) until the first date that recurrent or progressive disease was objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

       The duration of overall CR was measured from the time measurement criteria were first met for CR until the first date that progressive disease was objectively documented.

    b. Duration of stable disease: Stable disease was measured from the start of the treatment until the criteria for progression were met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

14. Progression-Free Survival: Progression-Free Survival (PFS) was defined as the duration of time from study entry to time of progression or death, whichever occured first.

15. Survival: Survival was defined as the duration of time from study entry to time of death or the date of last contact.

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Grade refers to the severity of the adverse event (AE). The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitlization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE.

Functional Assessment of Cancer Therapy – Ovarian - Trial Outcome Index (FACT-O TOI) Scale

FACT-O TOI Scale
HRQOL was measured using the Functional Assessment of Cancer Therapy (FACT) – Ovarian (FACT-O) questionnaire. [3] FACT-O, a multidimensional questionnaire, was developed and validated for patient with ovarian cancer. This questionnaire includes items from FACT–General (FACT-G; version 4) focused on general cancer patients and questions tailored to ovarian cancer patients (FACT-O subscale). Subscale was scored from 0 to 4 points where 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much. These subscales can be analyzed separately or aggregated to produce a total HRQOL score. Two of the FACT-G subscales (physical well-being and functional well-being) plus the FACT-O subscale can be combined as the Trial Outcome Index (TOI).

FACT/GOG-NTX Scale
Short- and long-term neurologic symptoms induced by platinum/paclitaxel drugs were measured with items from the FACT/GOG-Ntx subscale. [4]

FACT-GOG-AD Scale
The FACT-GOG-AD Scale was employed to measure abdominal symptoms. [5] A higher AD Subscale represents better QOL.

Functional Assessment of Cancer Therapy - clinically meaningful difference
The subscales FACT-G, FACT-O, Ntx, and AD, were each scored using a 5-point scale (0=not at all; 1=a little bit; 2=somewhat; 3=quite a bit; and 4=very much). The FACT-O score is the sum of the FACT-G score and FACT-O subscale score. Higher FACT-O scores are associated with better HRQOL.

We determined the magnitude of differences that is considered clinically meaningful. In FACT-O total score, a 6-point difference corresponds to the average improvement in ovarian cancer patients who show improvement in performance status over time. It also corresponds to approximately one-third standard deviation, which is considered to be in the likely range of an instrument’s minimally important difference.

Functional Assessment of Cancer Therapy – Ovarian - Trial Outcome Index (FACT-O TOI) Scale

Below is a list of statements that other people with you illnesses have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I have a lack of energy	0	1	2	3	4
I have nausea	0	1	2	3	4
Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
I have pain	0	1	2	3	4
I am bothered by side effects of treatment	0	1	2	3	4
I feel ill	0	1	2	3	4
I am forced to spend time in bed	0	1	2	3	4

FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I am able to work (include work at home)	0	1	2	3	4
My work (include work at home) is fulfilling	0	1	2	3	4
I am able to enjoy life	0	1	2	3	4
I have accepted my illness	0	1	2	3	4
I am sleeping well	0	1	2	3	4
I am enjoying the things I usually do for fun	0	1	2	3	4
I am content with the quality of my life right now	0	1	2	3	4

Additional concerns	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I have swelling in my stomach area.	0	1	2	3	4
I am losing weight	0	1	2	3	4
I have control of my bowels	0	1	2	3	4
I have been vomiting	0	1	2	3	4
I am bothered by hair loss	0	1	2	3	4
I have a good appetite	0	1	2	3	4
I like the appearance of my body	0	1	2	3	4
I am able to get around by myself	0	1	2	3	4
I am able to feel like a woman	0	1	2	3	4
I have cramps in my stomach area	0	1	2	3	4
I am interested in sex	0	1	2	3	4
I have concerns about my ability to have children	0	1	2	3	4
I have pain in my stomach area	0	1	2	3	4
Stomach pain interferes with my daily functioning	0	1	2	3	4

Functional Assessment of Cancer Therapy – Ovarian - Trial Outcome Index (FACT-O TOI) Scale (continued)

Below is a list of statements that other people with you illnesses have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

Other concerns	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I have numbness or tingling in my hands	0	1	2	3	4
I have numbness or tingling in my feet	0	1	2	3	4
I feel discomfort in my hands	0	1	2	3	4
I feel discomfort in my feet	0	1	2	3	4

References

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

2. Rustin GJ, Marples M, Nelstrop AE, Mahmoudi M, Meyer T. Use of CA-125 to define progression of ovarian cancer in patients with persistently elevated levels. J Clin Oncol 2001;19:4054-7.

3. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993;11:570-9.

4. Huang HQ, Brady MF, Cella D, Fleming G. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. Int J Gynecol Cancer 2007;17:387-93.

5. Wenzel L, Huang HQ, Cella D, Walker JL, Armstrong DK, Gynecologic Oncology G. Validation of FACT/GOG-AD subscale for ovarian cancer-related abdominal discomfort: a Gynecologic Oncology Group study. Gynecologic oncology 2008;110:60-4.

Table S1. Patient and Clinico-pathologic Characteristics According to Treatment Group.

Characteristic		Total	Weekly Paclitaxel +/- BEV (n=346)	Every 3 wk Paclitaxel +/- BEV (n=346)
Age <60 years		315 (46%)	156 (45%)*	159 (46%)
Race †	Non-Hispanic White	591 (85%)	298 (86%)	293 (85%)
	Non-Hispanic Black	38 (5%)	17 (5%)	21 (6%)
	Hispanic	27 (4%)	12 (4%)	15 (4%)
	Asian	14 (2%)	8 (2%)	6 (2%)
	Other	22 (3%)	11 (3%)	11 (3%)
Performance Status ‡	0	316 (46%)	158 (46%)	158 (46%)
	1	326 (47%)	166 (48%)	160 (46%)
	2	50 (7%)	22 (6%)	28 (8%)
Stage	II	18 (3%)	8 (2%)	10 (3%)
	III	464 (67%)	241 (70%)	223 (64%)
	IV	210 (30%)	97 (28%)	113 (33%)
Site of origin	Ovary	550 (79%)	269 (78%)	281 (81%)
	Fallopian tube	68 (10%)	36 (10%)	32 (9%)
	Peritoneum	74 (11%)	41 (12%)	33 (9%)
Size of Residual	Microscopic	166 (24%)	84 (24%)	82 (24%)
	Gross	438 (63%)	218 (63%)	220 (64%)
	Not assessed†	88 (13%)	44 (13%)	44 (13%)

Weekly Paclitaxel = dose dense weekly paclitaxel and every 3 week carboplatin
Every 3 wk Paclitaxel = Every 3 week paclitaxel and carboplatin
BEV= bevacizumab

Table S1. Patient and Clinico-pathologic Characteristics According to Treatment Group. (continued)

Characteristic		Total	Weekly Paclitaxel +/- BEV (n=346)	Every 3 wk Paclitaxel +/- BEV (n=346)
Histology §	Serous	611 (88%)	302 (87%)	309 (89%)
	Endometrioid	16 (2%)	8 (2%)	8 (2%)
	Clear Cell	18 (3%)	11 (3%)	7 (2%)
	Mucinous	7 (1%)	3 (1%)	4 (1%)
	Others	40 (6%)	22 (6%)	18 (5%)
Grade	1	27 (4%)	19 (5%)	8 (2%)
	2	68 (10%)	30 (9%)	38 (11%)
	3	595 (86%)	296 (85%)	299 (86%)
	Other/not specified	20 (3%)	12 (3%)	8 (2%)
Opted for bevacizumab	Yes	580 (84%)	291 (84%)	289 (83%)
	No	112 (16%)	55 (16%)	57 (17%)
Opted for neoadjuvant	Yes	88 (13%)	44 (13%)	44 (13%)
	No	604 (87%)	302 (87%)	302 (87%)

Weekly Paclitaxel = dose dense weekly paclitaxel and every 3 week carboplatin
Every 3 wk Paclitaxel = Every 3 week paclitaxel and carboplatin
BEV= bevacizumab
* Percentages may not sum to 100 because of rounding.
† Race or ethnic group was self-reported.
‡ A Gynecologic Oncology Group (GOG) performance status score = 0 is fully active, 1 is restricted in physically strenuous activities but ambulatory, and 2 is ambulatory and capable of self-care but unable to work.
† The size of residual disease was not assessed in patients who underwent neoadjuvant therapy.
§ Histologic type and tumor grade were obtained from the GOG Pathology Committee. All clear-cell tumors were classified as grade 3.
Significance levels for the comparison of baseline variables have not been computed because of the use of minimization in treatment assignment.

Table S2. Clinical Characteristics for Patients Who Opted for Bevacizumab vs. No Bevacizumab

	Bevacizumab			
	Yes (n=580)		No (n=112)	
	N	%	N	%
Age < 60 Years				
< 60	269	46.4	46	41.1
>=60	311	53.6	66	58.9
Race				
Non Hispanic Black	28	4.8	10	8.9
Non Hispanic White	499	86.0	92	82.1
Hispanic	22	3.8	5	4.5
Asian/Pacific Islander	11	1.9	3	2.7
Other	20	3.4	2	1.8
Performance Status				
0	274	47.2	42	37.5
1	265	45.7	61	54.5
2	41	7.1	9	8.0
Stage				
II	13	2.2	5	4.5
III	390	67.2	74	66.1
IV	177	30.5	33	29.5
Site of Disease				
Ovary	459	79.1	91	81.3
Fallopian Tube	56	9.7	12	10.7
Peritoneum	65	11.2	9	8.0

Table S2. Clinical Characteristics for Patients Who Opted for Bevacizumab vs. No Bevacizumab (continued)

	Bevacizumab			
	Yes (n=580)		No (n=112)	
	N	%	N	%
Size of Residual Disease				
Microscopic	134	23.1	32	28.6
Gross residual	372	64.1	66	58.9
Neo-adjuvant	74	12.8	14	12.5
Histology				
Clear Cell	12	2.1	6	5.4
Endometrioid	14	2.4	2	1.8
Mucinous	6	1.0	1	0.9
Papillary Serous	513	88.4	98	87.5
Other/Not specified	35	6.0	5	4.5
Grade				
1	25	4.3	2	1.8
2	59	10.2	9	8.0
3	494	85.2	101	90.2
Other/Not Specified	2	0.3		

Every 3 wk Paclitaxel = Every 3 wk Paclitaxel and carboplatin
Weekly Paclitaxel = dose dense weekly paclitaxel and every 3 week carboplatin

Table S3. Clinical Characteristics for Patients Who Opted for Bevacizumab: Weekly Paclitaxel vs. Every 3 wk Paclitaxel

	Regimen					
	Weekly Paclitaxel		**Every 3 wk Paclitaxel**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Age < 60 Years						
< 60	134	46.0	135	46.7	269	46.4
>=60	157	54.0	154	53.3	311	53.6
Race						
Non Hispanic Black	14	4.8	14	4.8	28	4.8
Non Hispanic White	255	87.6	244	84.4	499	86.0
Hispanic	7	2.4	15	5.2	22	3.8
Asian/Pacific Islander	6	2.1	5	1.7	11	1.9
Other	9	3.1	11	3.8	20	3.4
Performance Status						
0	137	47.1	137	47.4	274	47.2
1	137	47.1	128	44.3	265	45.7
2	17	5.8	24	8.3	41	7.1
Stage						
II	4	1.4	9	3.1	13	2.2
III	202	69.4	188	65.1	390	67.2
IV	85	29.2	92	31.8	177	30.5
Site of Disease						
Ovary	222	76.3	237	82.0	459	79.1
Fallopian Tube	33	11.3	23	8.0	56	9.7
Peritoneum	36	12.4	29	10.0	65	11.2

Table S3. Clinical Characteristics for Patients Who Opted for Bevacizumab: Weekly Paclitaxel vs. Every 3 wk Paclitaxel (continued)

	Regimen					
	Weekly Paclitaxel		Every 3 wk Paclitaxel		Total	
	N	N	N	%	N	%
Size of Residual Disease						
Microscopic	67	23.0	67	23.2	134	23.1
Gross residual	187	64.3	185	64.0	372	64.1
Neo-adjuvant	37	12.7	37	12.8	74	12.8
Histology						
Clear Cell	8	2.7	4	1.4	12	2.1
Endometrioid	7	2.4	7	2.4	14	2.4
Mucinous	3	1.0	3	1.0	6	1.0
Papillary Serous	255	87.6	258	89.3	513	88.4
Other/Not specified	18	6.2	17	5.9	35	6.0
Grade						
1	17	5.8	8	2.8	25	4.3
2	25	8.6	34	11.8	59	10.2
3	248	85.2	246	85.1	494	85.2
Other/Not Specified	1	0.3	1	0.3	2	0.3
Opted for Bevacizumab						
Yes	291	100.0	289	100.0	580	100.0
Opted for NeoAdjuvant						
No	254	87.3	252	87.2	506	87.2
Yes	37	12.7	37	12.8	74	12.8
Total	291	50.2	289	49.8	580	100.0

Every 3 wk Paclitaxel = Every 3 week paclitaxel and carboplatin

Weekly Paclitaxel = dose dense weekly paclitaxel and every 3 week carboplatin

Table S4. Clinical Characteristics for Patients Who Did Not Opt for Bevacizumab: Weekly Paclitaxel vs. Every 3 wk Paclitaxel

Characteristic	Regimen					
	Weekly Paclitaxel	Every 3 wk Paclitaxel			Total	
	N	N	N	%	N	%
Age < 60 Years						
< 60	22	40.0	24	40.0	46	41.1
>=60	33	60.0	33	60.0	66	58.9
Race						
Non Hispanic Black	3	5.5	7	5.5	10	8.9
Non Hispanic White	43	78.2	49	78.2	92	82.1
Hispanic	5	9.1	0	9.1	5	4.5
Asian/Pacific Islander	2	3.6	1	3.6	3	2.7
Other	2	3.6	0	3.6	2	1.8
Performance Status						
0	21	38.2	21	38.2	42	37.5
1	29	52.7	32	52.7	61	54.5
2	5	9.1	4	9.1	9	8.0
Stage						
II	4	7.3	1	7.3	5	4.5
III	39	70.9	35	70.9	74	66.1
IV	12	21.8	21	21.8	33	29.5
Site of Disease						
Ovary	47	85.5	44	85.5	91	81.3
Fallopian Tube	3	5.5	9	5.5	12	10.7
Peritoneum	5	9.1	4	9.1	9	8.0

Table S4. Clinical Characteristics for Patients Who Did Not Opt for Bevacizumab: Every 3 wk Paclitaxel vs. Weekly Paclitaxel (continued)

Characteristic	Regimen					
	Weekly Paclitaxel		Every 3 wk Paclitaxel		Total	
	N	%	N	%	N	%
Size of Residual Disease						
Microscopic	17	30.9	15	26.3	32	28.6
Gross residual	31	56.4	35	61.4	66	58.9
Neo-adjuvant	7	12.7	7	12.3	14	12.5
Histology						
Clear Cell	3	5.5	3	5.3	6	5.4
Endometrioid	1	1.8	1	1.8	2	1.8
Mucinous	0	0	1	1.8	1	0.9
Papillary Serous	47	85.5	51	89.5	98	87.5
Other/Not specified	4	7.3	1	1.8	5	4.5
Grade						
1	2	3.6	0	0	2	1.8
2	5	9.1	4	7.0	9	8.0
3	48	87.3	53	93.0	101	90.2
Opted for Bevacizumab						
No	55	100.0	57	100.0	112	100.0
Opted for NeoAdjuvant						
No	48	87.3	50	87.7	98	87.5
Yes	7	12.7	7	12.3	14	12.5
Total	55	49.1	57	50.9	112	100.0

Every 3 wk Paclitaxel = Every 3 week paclitaxel and carboplatin

Weekly Paclitaxel = dose dense weekly paclitaxel and every 3 week carboplatin

Table S5. Patients Ineligible for Study by Treatment Group: Weekly Paclitaxel vs. Every 3 wk Paclitaxel

	Regimen			
	Weekly Paclitaxel		Every 3 wk Paclitaxel	
	N	*%*	*N*	*%*
Eligible	336	97.1	334	96.5
Ineligible				
Invalid stage	3	0.9	1	0.3
Second primary	0	0	2	0.6
Invalid histology	2	0.6	1	0.3
Invalid primary site	4	1.2	5	1.4
Improper surgery	1	0.3	3	0.9
Total	346	50.0	346	50.0

Every 3 wk Paclitaxel = Every 3 week paclitaxel and carboplatin
Weekly Paclitaxel = dose dense weekly paclitaxel and every 3 week carboplatin

Table S6. Patients Completing Chemotherapy at Each Cycle of Treatment.

6a) Number of Patients Receiving Carboplatin at each Cycle of Treatment

	Not Choosing bevacizumab		**Choosing Bevacizumab**	
	Weekly Paclitaxel n (%)	**Every 3 wk Paclitaxel n (%)**	**Weekly Paclitaxel n (%)**	**Every 3 wk Paclitaxel n (%)**
Patients Enrolled	55	57	291	289
Cycle 1	53 (96)	55 (96)	286 (98)	287 (99)
Cycle 2	53 (96)	52 (91)	280 (96)	282 (97)
Cycle 3	53 (96)	52 (91)	275 (94)	280 (97)
Cycle 4	51 (93)	51 (89)	264 (91)	275 (95)
Cycle 5	50 (91)	51 (89)	255 (88)	271 (94)
Cycle 6	46 (83)	48 (84)	242 (83)	266 (92)

6b) Number of Patients Receiving a Taxane (Paclitaxel or Docetaxel) at Each Cycle of Treatment

	Not Choosing bevacizumab		**Choosing Bevacizumab**	
	Weekly Paclitaxel n (%)	**Every 3 wk Paclitaxel n (%)**	**Weekly Paclitaxel n (%)**	**Every 3 wk Paclitaxel n (%)**
Patients Enrolled	55	57	291	289
Cycle 1	53 (96)	55 (96)	285 (98)	287 (99)
Cycle 2	53 (96)	52 (91)	278 (95)	281 (97)
Cycle 3	53 (96)	52 (91)	273 (94)	280 (97)
Cycle 4	51 (93)	51 (89)	262 (90)	273 (94)
Cycle 5	50 (91)	50 (88)	251 (86)	268 (93)
Cycle 6	47 (85)	48 (84)	236 (81)	264 (91)

Every 3 wk Paclitaxel = Every 3 week paclitaxel and carboplatin
Weekly Paclitaxel = dose dense weekly paclitaxel and every 3 week carboplatin
Chemotherapy was administered during cycles 1 through 6. The percent of the paclitaxel dose delivered to those randomized to the Every 3 wk Paclitaxel was 89.3% compared to 79.5% in the Weekly Paclitaxel over the first 150 days following randomization.

Table S7. Patients Discontinued Protocol Therapy by Treatment Group: Every 3 wk Paclitaxel vs. Weekly Paclitaxel

	Regimen				
	Weekly Paclitaxel		Every 3 wk Paclitaxel		Total
	N	%	N	%	N
Completed protocol treatment (at least 6 cycles)	291	84.1	314	90.8	605
Discontinued protocol treatment	55	15.9	32	9.2	87
Reason for Discontinuation					
Disease progression	3	0.9	6	1.7	9
Patient withdrawal	9	2.6	6	1.7	15
Adverse events	33	9.5	12	3.5	45
Death	7	2.0	8	2.3	15
Other reason	3	0.9	0	0	3
Total	346	50.0	346	50.0	692

Every 3 wk Paclitaxel = Every 3 week paclitaxel and carboplatin

Weekly Paclitaxel = dose dense weekly paclitaxel and every 3 week carboplatin

Table S8. Patients with Treatment Delay by Treatment Group: Every 3 week Paclitaxel vs. Weekly Paclitaxel

	Regimen			
	Weekly Paclitaxel		Every 3 wk Paclitaxel	
	N	%	N	%
No Delay	139	40.9	215	62.7
Yes Delay (at least one during cycles 1-6)	201	59.1	128	37.3
Reason Cycle Delayed				
Adverse Event	149	43.8	75	21.9
Non Protocol Illness	17	5.0	19	5.5
Personal Reason	11	3.2	13	3.8
Scheduling difficulty	24	7.1	21	6.1
Total*	340	49.8	343	50.2

* Does not include those individuals who did not initiate study treatment.
Every 3 wk Paclitaxel = Every 3 week paclitaxel and carboplatin
Weekly Paclitaxel = dose dense weekly paclitaxel and every 3 week carboplatin

Figure S2. Quality of Life Analyses.
Panel a. Patient reported FACT-O TOI – Primary Endpoint. Patients received Weekly Paclitaxel reported lower scores in FACT-O TOI during assessment period compared to those receiving Every 3 week Paclitaxel. The maximum decrease in FACT-O TOI score was 2.7 points (97.5% CI: -5.44~-0.02; p=0.024) at 3 weeks after completion of six cycles of chemotherapy.

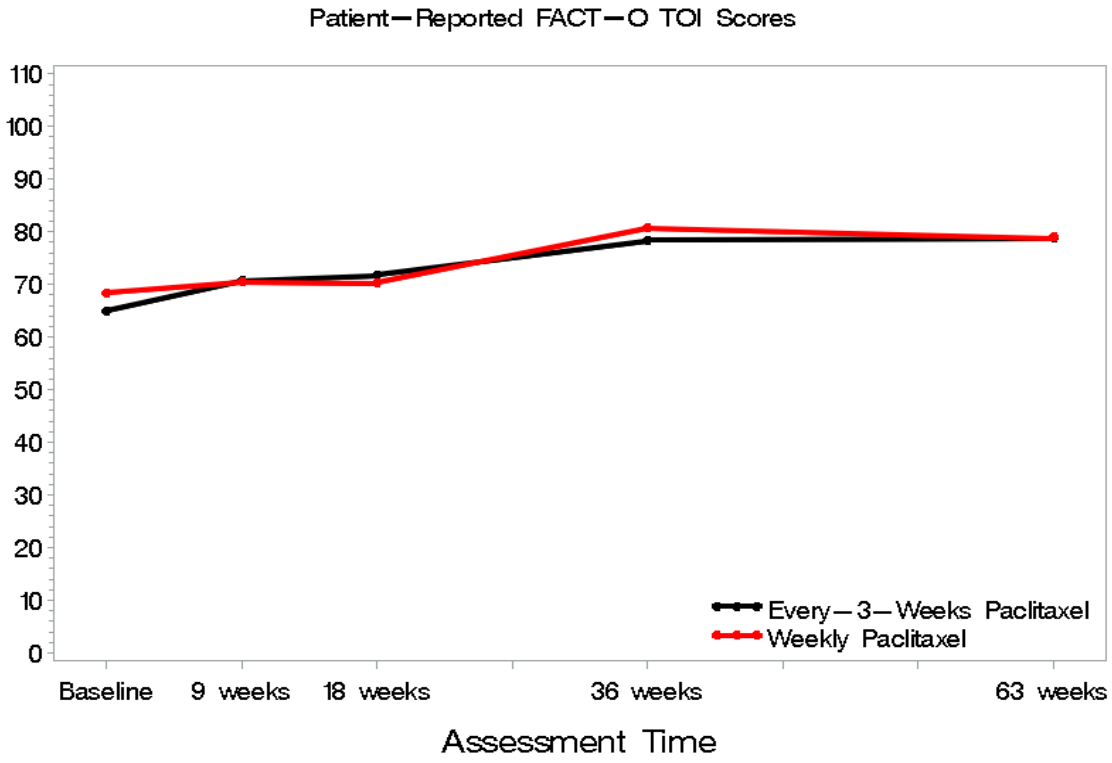


Figure S2. Quality of Life Analyses. (continued)

Panel b. Patient reported FACT-O TOI – Primary Endpoint. Dose dense weekly paclitaxel was associated with worse neurotoxicity peaking at the end of cycle 6 and persisting into one year after treatment.

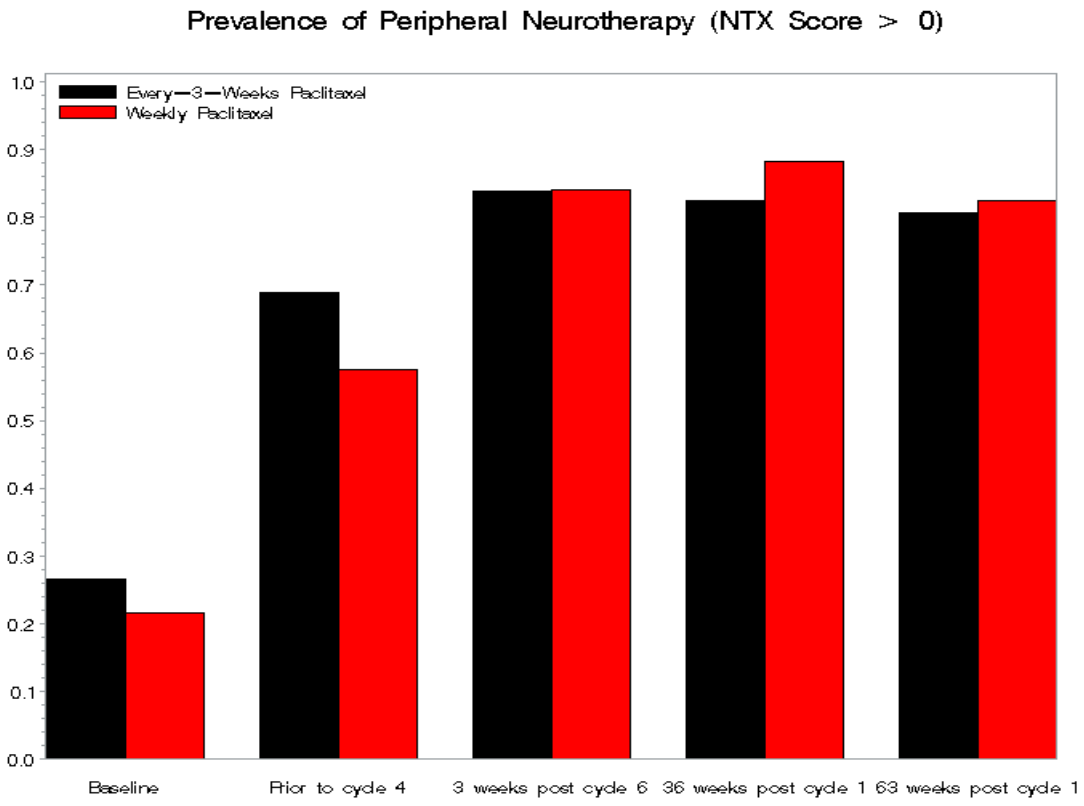


Figure S2. Quality of Life Analyses. (continued)

Panel c. Severity of reported neurotoxicity scores